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EP-A- 0 230 944 EP-A- 0 260 605
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PATENT ABSTRACTS OF JAPAN vol. 9, no. 188 (C-295)(1911), 03 August 1985*

CHEMICAL ABSTRACTS, vol. 107, no. 23, 07 December 1987, Columbus, OH (US); A. ZIDERMANE et al., p. 20, no. 211535u*

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CHEMICAL ABSTRACTS, vol. 102, no. 9, 04
March 1985, Columbus, OH (US); I. BUIKIS et
al., p. 25, no. 89746t*

CHEMICAL ABSTRACTS, vol. 98, no. 21, 23
May 1983, Columbus, OH (US); J. ULDRIKIS
et al., p. 640, no. 179181h*

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Description

The present invention relates to an agent for enhancing the drug effects of an antitumor drug, which comprises a pyridine derivative or a pharmaceutically acceptable salt thereof, as an active ingredient.

5 Remarkable developments have been observed in the chemotherapy of cancer. There have been an increasing number of cases in which some of cancers have been reportedly completely healed. However, there are still a number of problems yet to be solved. Among them, to reduce the side effects, to overcome drug resistance against antitumor drugs and to prevent relapse and metastasis are problems which are desired to be solved as soon as possible. Further, no antitumor drugs have been developed which are truly
10 effective against solid cancers such as carcinoma of the colon, cancer of the stomach and carcinoma of the esophagus.

In the clinical field, it is frequently experienced that antitumor drugs which were initially effective, tend to be non-effective during an extended period of treatment. Further, when a tumor metastasizes or recurs, an antitumor agent is no longer effective in many cases.

15 Among various factors attributable to such tendency, it is known to be an important factor that cancer cells acquire drug resistance against antitumor drugs.

Yet, it frequently happens that cancer cells which acquired drug resistance against a certain particular antitumor drug, also show resistance against many other antitumor drugs which are totally different from the particular antitumor drug in their chemical structures or functional mechanisms (multidrug resistance), which
20 constitutes a serious obstacle in the chemotherapy of cancer.

The study on the multidrug resistance against antitumor drugs has been rapidly progressed in recent years, and a part of the mechanism has been made clear. Namely, in the cancer cells which acquire resistance, an increase of a certain P-glycoprotein is observed which has a function of a drug efflux pump, whereby the antitumor drug is pumped out of the cells in an energy dependent fashion, and consequently,
25 the concentration of the antitumor agent in the cells decreases.

Tsuruo et al have found that Verapamil i.e. one of calcium antagonistic drugs overcomes the multidrug resistance against antitumor drugs (see Cancer Res. 41; 1967-1972 (1981)).

Akasawa et al have reported that calcium antagonistic drug nifedipine enhances the antitumor activities of vincristine sulfate (Cancer and Chemotherapy, vol. 11, 943-947 (1984)). It has also been reported that
30 calcium antagonistic drug diltiazem enhances the drug effects of vincristine (VCR) (see Japanese Unexamined Patent Publication No. 208222/1983).

These three drugs are all calcium antagonistic substances, but they have no structural similarity at all. Further, it is known that there is no relationship between the strength of the calcium antagonistic effects and the strength of the effects for enhancing the drug effects of the antitumor drugs.

35 Further, certain dihydropyridine compounds are known to increase the sensitivity of cancer cells to carcinostatic drugs (see Japanese Unexamined Patent Publication No. 135381/1988) or to be effective for preventing metastasis of cancer (Japanese Unexamined Patent Publication No. 87516/1987).

It has already been known that 1,4-dihydropyridines among the compounds of the present invention have strong vasodilator activities by calcium antagonism, and they are useful as pharmaceuticals effective
40 against hypertension, angina pectoris or disorder of cerebral circulation (U.S. Patents 3,485,847, 3,644,627, 3,985,758 and 4,576,934, EP-A-0 221 382 and EP-A-0 123 850, JP-A-6 056 956).

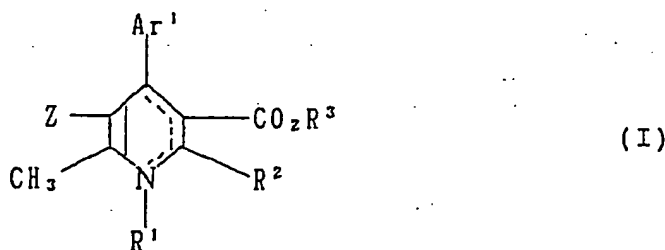
On the other hand, substantially nothing has been known with respect to the biological activities of the pyridines of the present invention.

The present inventors have found surprisingly that the compounds of the formula I as defined
45 hereinafter and their pharmaceutically acceptable salts are effective not only to suppress or diminish the drug resistance against cancer cells which acquired the drug resistance against antitumor drugs, but also to enhance the drug effects of antitumor drugs against cancer cells having no resistance. The present invention has been accomplished on the basis of this discovery.

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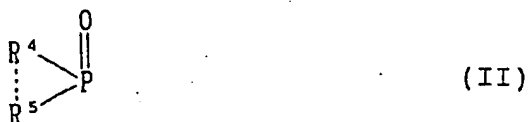
The present invention provides the use of a compound of the formula I:



wherein Ar¹ is phenyl, pyridyl, furyl or 2,1,3-benzooxadiazol-4-yl, which may be substituted by one or two substituents selected from the group consisting of NO₂, CF₃, Br, Cl, F, R⁶ (wherein R⁶ is C₁-C₄ alkyl), OH, OR⁶, OCHF₂, COOR⁶, NH₂, NHR⁶, NR⁶R⁷ (wherein R⁷ has the same meaning as R⁶), CONH₂, CONHR⁶, CONR⁶R⁷, COSR⁶, SR⁶, S(O)R⁶, S(O)₂R⁶, SO₃H, SO₃R⁶, SO₂NH₂, SO₂NHR⁶, SO₂NR⁶R⁷, CN and phenyloxy;

the nitrogen-containing hetero ring portion represents a 1,4-dihydropyridine ring or a pyridine ring;

Z is a group of the formula II:



wherein each of R⁴ and R⁵ which may be the same or different is OH, C₁-C₁₂ linear or branched primary or secondary alkyloxy, C₃-C₆ linear or branched unsaturated alkyloxy, C₃-C₆ cycloalkyloxy, C₁-C₆ alkoxy substituted by C₃-C₆ cycloalkyl, OAr² (wherein Ar² is phenyl which may be substituted by halogen, C₁-C₃ alkyl or C₁-C₃ alkoxy), OANR⁶R⁷ (wherein A is C₂-C₆ alkylene which may be substituted by C₁-C₃ alkyl or Ar²), OAN(CH₂Ar²)R⁶, OAR⁶, OACN, NH₂, NHR⁶, NR⁶R⁷, 1-piperidinyl or 1-pyrrolidinyl, or R⁴ and R⁵ together form OYO (wherein Y is C₂-C₄ linear alkylene which may be substituted by R⁶, CO₂R⁶, OR⁶ or A), NHYO, R⁶NYO, NHYNH, R⁶NYNH or R⁶NYNR⁷, or Z is CO₂R⁸ (wherein R⁸ has the same meaning as R³ defined hereinafter);

R¹ is present only when the nitrogen-containing hetero ring is a 1,4-dihydropyridine ring, and it is H, R⁶, ANR⁶R⁷, AN(CH₂CH₂)₂O, AOR⁶ or CH₂phenyl;

R² is R⁶, Ar², Ar²CH=CH, Ar²CH(OH)CH₂, CHO, CN, CH₂OH, CH₂OR⁶, CH₂CH₂N(CH₂CH₂)₂NR⁶, NH₂, NHR⁶ or NR⁶R⁷;

R³ is hydrogen, C₁-C₁₂ linear or branched alkyl, C₃-C₆ linear or branched unsaturated alkenyl or alkynyl, C₃-C₆ cycloalkyl, C₁-C₆ alkyl substituted by C₃-C₆ cycloalkyl, AOR⁶, AO(CH₂)ₘAr² (wherein m is an integer of from 0 to 3), (CH₂)ₘAr², ANH₂, ANHR⁶, ANR⁶R⁷, ANR⁶(CH₂)ₘAr², AN{(CH₂)ₘAr²}{(CH₂)ₙAr³} (wherein n has the same meaning as m, and Ar³ has the same meaning as Ar²), 1-benzyl-4-piperidinyl, 1-benzyl-2-piperidinyl, 2-pyridinylmethyl, 3-pyridinylmethyl, AQ (wherein Q is pyrrolidine or piperidine which may be substituted by (CH₂)ₘAr²), 4-R⁶-1-piperazinyl, 4-Ar²-1-piperazinyl, 4-(Ar²)₂CH-1-piperazinyl or 4-(Ar²)₂CH-1-(1,4-diazacycloheptyl);

or a pharmaceutically acceptable salt of the compound for the manufacture of an agent for enhancing the drug effect at an antitumor drug.

In this specification, "the compound of the present invention" refers generally to not only the compound of the formula I but also to the pharmaceutically acceptable salt thereof.

Now, the various substituents in the formula I for the compound of the present invention will be described specifically.

R¹ includes, for example, methyl, ethyl, methoxymethyl, methoxyethyl, aminoethyl, dimethylaminoethyl and benzyl.

R² includes, for example, methyl, phenyl, styryl, cyano, amino, methylamino, dimethylamino and hydroxymethyl.

R³ includes, for example, hydrogen, methyl, ethyl, n- and i-propyl, n-, i- and sec-butyl, n-pentyl, n-hexyl, n-octyl, n-decyl, cyclopropyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclopropylethyl, cyclohexylmethyl, cyclohexylethyl, allyl, 1-methylallyl, 2-methylallyl, 3-methylallyl, 2-propynyl, 3-butyryl, phenyl, p-chlorophenyl, p-methoxyphenyl, benzyl, p-chlorobenzyl, p-methoxybenzyl, phenethyl, p-chlorophenethyl, p-methoxyphenethyl, methoxyethyl, ethoxyethyl, i-propoxyethyl, dimethylaminoethyl, benzylmethylaminopropyl, benzyloxyethyl, n-propoxyethyl, cyanoethyl, methylaminoethyl, aminoethyl, benzylmethylaminoethyl, benzylphenylaminoethyl, 1-benzylpyridino-4-yl, 1-benzylpiperidino-2-yl, 2-pyridinomethyl, 4-diphenylmethyl-1-piperadinoethyl, 4-methyl-1-piperadinoethyl, 4-phenyl-1-piperadinoethyl, 2-oxopropyl and methylthioethyl.

Each of R⁴ and R⁵ includes, for example, hydroxy, methoxy, ethoxy, n- and i-propoxy, n-, i- and sec-butoxy, n-pentyloxy, n-hexyloxy, n-octyloxy, n-decyloxy, cyclopropyloxy, cyclopentyloxy, cyclohexyloxy, cyclopropylmethoxy, cyclopropylethoxy, cyclohexylmethoxy, cyclohexylethoxy, allyloxy, 1-methylallyloxy, 2-methylallyloxy, 3-methylallyloxy, 2-propynoxy, 3-butyloxy, phenyloxy, p-chlorophenyloxy, p-methoxyphenyloxy, benzyloxy, p-chlorobenzyloxy, p-methoxybenzyloxy, phenethyloxy, p-chlorophenethyloxy, p-methoxyphenethyloxy, methoxyethyloxy, ethoxyethyloxy, i-propoxyethyloxy, dimethylaminoethyloxy, benzylmethylaminopropoxy, benzyloxyethyloxy, n-propoxyethyloxy, cyanoethyloxy, amino, methylamino, diisopropylamino, 1-piperidinyl and 1-pyrrolidinyl.

The case where R⁴ and R⁵ together form a ring includes, for example, 1,2-dimethylethylenedioxy, 1,3-propylenedioxy, 2,2-dimethyl-1,3-propylenedioxy, 1,3-dimethyl-1,3-propylenedioxy, 2,2-diethyl-1,3-propylenedioxy, 2-ethyl-1,3-propylenedioxy, 2-isopropyl-1,3-propylenedioxy, 2-cyclobutyl-1,3-propylenedioxy, 2-cyclohexyl-1,3-propylenedioxy, 2,2-diethoxy-1,3-propylenedioxy, 1,1,3,3-tetramethyl-1,3-propylenedioxy, 1,4-dimethyl-1,4-butylenedioxy, 2-dihydro-1,4-butylenedioxy, N-methyl-1,3-dimethylpropyleneaminoxy, N-methyl-1-methylethyleneaminoxy, N,N'-dimethylethylenediamino and N,N'-diethylethylenediamino.

Ar¹ includes, for example, phenyl, nitrophenyl, chlorophenyl, fluorophenyl, trifluoromethylphenyl, hydroxyphenyl, methoxyphenyl, methoxycarbonylphenyl, aminophenyl, methylaminophenyl, dimethylaminophenyl, aminocarbonylphenyl, methylaminocarbonylphenyl, dimethylaminocarbonylphenyl, methylphenyl, methylthiocarbonylphenyl, methylthiophenyl, methylsulfonylphenyl, sulfonylphenyl, methoxysulfonylphenyl, aminosulfonylphenyl, methylaminosulfonylphenyl, dimethylaminosulfonylphenyl and o-, m- and p-substituted cyanophenyl, 2,3-dichlorophenyl and 2,1,3-benzooxadiazol-4-yl.

Among the compounds of the present invention, those of the formula I wherein either one of substituents R¹, R², R³, R⁴ and R⁵ contains at least one basic nitrogen atom capable of forming a salt, or pharmaceutically acceptable salts thereof are preferred, since they present preferred drug effect-enhancing agents for antitumor drugs.

Among the compounds of the present invention, those wherein the nitrogen-containing hetero ring is a 1,4-dihydropyridine ring, are covered by the following Japanese Unexamined Patent Publications and can be prepared in accordance with the method disclosed in these publications.

Japanese Unexamined Patent Publications No. 161392/1984, No. 69089/1985, No. 248693/1985, No. 258194/1985, No. 27995/1986, No. 30591/1986, No. 37793/1986, No. 63688/1986, No. 63689/1986, No. 210092/1986, No. 254596/1986, No. 257995/1986, No. 169795/1987, No. 195392/1987, No. 68591/1988, No. 115889/1988, No. 115890/1988 and No. 115891/1988.

Among the compounds of the present invention, those wherein the nitrogen-containing hetero ring is a pyridine ring, include new compounds. However, such compounds may readily be obtained by treating the corresponding 1,4-dihydropyridine derivatives with an oxidizing agent such as nitric acid, nitrous acid or chromic acid.

As described hereinafter, the compounds of the present invention enhance the drug effects of antitumor drugs not only against cancer cells which acquired drug resistance but also against cancer cells having no drug resistance. Therefore, they provide excellent advantages such that the dose of antitumor drugs to patients can be reduced, and toxicity or side effects can be reduced. Further, cross resistance can be overcome, which provides an important advantage that the number of useful antitumor drugs increases so that antitumor drugs can be selected to meet the symptoms and conditions of the patients. Recurrence of cancer is one of serious problems in the clinical field of chemotherapy of cancer. In many cases, this is regarded as a state where slightly remained drug resistant tumor cells have again proliferated.

The compounds of the present invention are capable of diminishing drug resistance when used in combination with antitumor agents, and they thus can be used to prevent recurrence by killing all the tumor cells and completely healing the tumor. Further, the compounds of the present invention may be employed to prevent metastasis. The enhancement of the drug effects of antitumor drugs by the combined use of the compounds of the present invention and the antitumor agents is expected also against solid cancer such as lung cancer, liver cancer or carcinoma of the colon to which the conventional antitumor agents used to be

hardly effective due to formation of multidrug resistant gene (see Fojo et al, Cancer Res., 45,3002-3007 (1986)).

The compounds of the present invention can be administered orally (in the form of tablets, pills, powders, capsules, granules, etc.) or parenteral (in the form of injection drugs, intravenous drip infusion drugs, suppositories, etc.). Further, compounds of the present invention may be administered alone or in admixture with antitumor drugs.

The dose of the compound of the present invention varies depending upon the manner of administration, the age of the patient, the type of disease, the diseased condition and the type of concurrently used antitumor agents. However, the dose is usually from 0.01 to 3 g, preferably from 0.05 to 1 g, per day for an adult. There is no particular restriction as to the concurrently used antitumor drugs. However, vina alkaloids represented by vincristine and vinblastine, adriamycin, actinomycin-D, daunomycin and colchicine may be mentioned as preferred examples.

These antitumor agents may be administered in such a dose and in such a dosage form as usually employed clinically, and they may be administered simultaneously with the compound of the present invention, or before or after the administration of the compound of the present invention. Various formulations may be employed for the oral administration of the active component of the present invention. For example, the active component may be formulated into tablets, granules, fine particles, powders, syrups or elixirs. Granules and powders may be filled in capsules to obtain unit dosage formulations, as the case requires.

Among such drug formulations for oral administration, solid drugs may contain an excipient such as silicic anhydride, metasilicic acid, magnesium aluminate, synthetic aluminum silicate, lactose, sucrose, corn starch, fine crystalline cellulose or hydroxypropyl starch, a binder such as gum arabic, gelatin, tragacanth, hydroxypropyl cellulose or polyvinyl pyrrolidone, a lubricant such as magnesium stearate, talc or silica, a disintegrator such as potato starch or calcium carboxymethyl cellulose, or a wetting agent such as polyethylene glycol, sorbitan monooleate, polyoxyethylene hardened castor oil or sodium lauryl sulfate.

Tablets may be coated in accordance with a conventional method.

Among the drugs for oral administration, liquid formulations may be in the form of aqueous or oily emulsions or syrups, or may be formulated in a dry product which is capable of being dissolved with a suitable vehicle prior to its use. Such liquid formulations may contain commonly employed additives, for example, an assisting agent for emulsification such as sorbit syrup, methyl cellulose, gelatin or hydroxyethyl cellulose, an emulsifier such as lecithin sorbitan monooleate or polyoxyethylene hardened castor oil, a non-aqueous vehicle such as a fractionated coconut oil, almond oil or peanut oil, or an antiseptic such as methyl p-hydroxybenzoate, propyl p-hydroxybenzoate or sorbic acid.

These drugs for oral administration may further contain a preservative or a stabilizer, as the case requires.

When the active component of the present invention is formulated into an injection drug, it may take a form of an oil solution, an emulsion or an aqueous solution. Such liquid formulations may contain an emulsifier, a stabilizer, etc. which are commonly employed.

Depending upon the manner of administration, these drugs may contain at least 1% by weight, preferably from 5 to 50% by weight, of the active ingredient.

Further, the active ingredient of the present invention may be formulated into a suppository by a usual method.

Now, Test Examples will be given to show the drug effect-enhancing activities of the compounds of the present invention for antitumor agents.

TEST EXAMPLE 1

MTT colorimetric assay performed in a 96-well plate was used for an in vitro chemosensitivity test. The assay is dependent on the reduction of MTT by the mitochondrial dehydrogenase of viable cells to a blue formazan product which can be measured spectrophotometrically. Equal numbers of cells (2,000 for KB-3-1 and 5,000 for KB-C2) were inoculated into each well with 0.18 ml of culture medium. After overnight incubation (37°C, 5% CO₂), 20 µl of vincristine solution and 0.5 µl of sample solution were added and incubated for 4 days. Then, 50 µl of MTT (1.1 mg/ml PBS) was added to each well and incubated for further 4 hours. The resulting formazan was dissolved with 100 µl of DMSO after aspiration of the culture medium. Plates were placed on a plate shaker for 5 minutes and read immediately at 570 nm. IC₅₀ (ng/ml) with a tested sample 10 µM is given in Table 1; and IC₅₀ of vincristine without a sample was 5,000 ng/ml.

MTT: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide

MEM: minimum essential medium

The test results are shown in Table 1.

Table 1

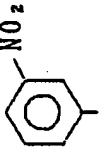
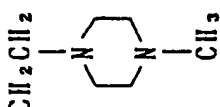
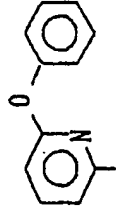
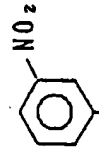
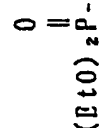
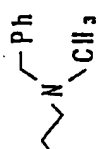
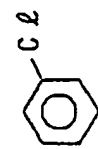
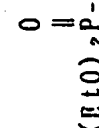
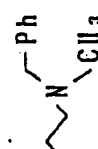
Ar ¹	Z	R ¹	R ²	R ³	IC ₅₀
	CO ₂ Et	H		Et	5
	CO ₂ Me	H	CH ₃	Me	120
		H	CH ₃		30
		H	CH ₃		12

Table 1 (continued)


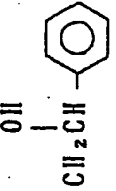
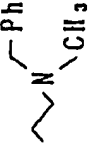

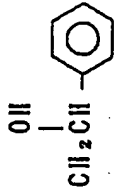
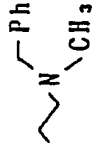
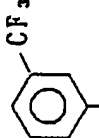

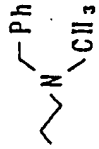

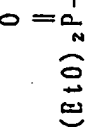
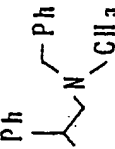
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	CO ₂ Me				6
	CO ₂ Me				27
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	 (EtO) ₂ P(=O)-		CH ₃		<5

Table 1 (continued)

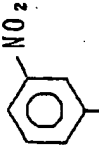

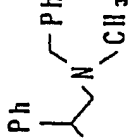
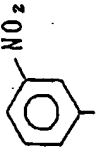
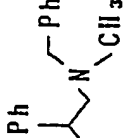
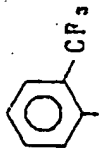
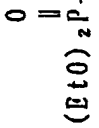
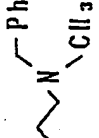
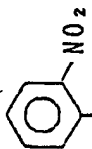
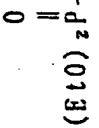
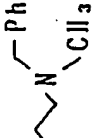
Ar ¹	Z	R ¹	R ²	R ³	IC ₅₀
		II	CH ₃		<5
	CO ₂ CH ₃	II	CH ₃		13
		II	CH ₃		5
		II	CH ₃		19

Table 1 (continued)

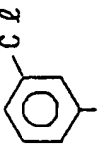
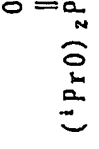
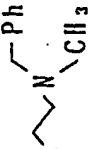
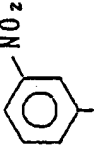
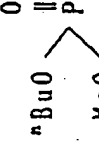
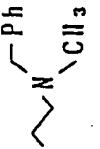
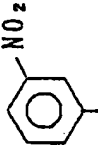
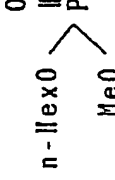
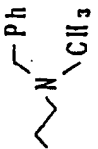
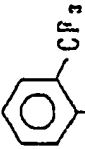
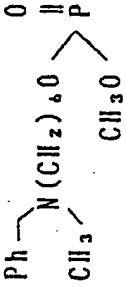
Ar ¹	Z	R ¹	R ²	R ³	IC ₅₀
		II	CH ₃		6
		II	CH ₃		6
		II	CH ₃		6
		II	CH ₃	CH ₃	<5

Table 1 (continued)

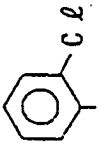
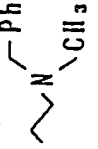
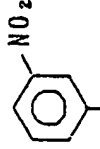
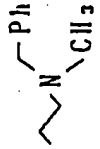
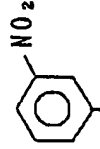
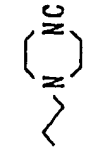
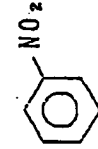
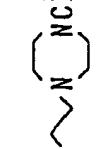
Ar ¹	Z	R ¹	R ²	R ³	IC ₅₀
	$\text{CH}_3\text{O}-\text{CH}_2-\text{O}-\text{P}(=\text{O})(\text{CH}_3)(\text{CH}_2)_5\text{O}$		CH ₃		6
	$\text{CH}_3\text{O}-\text{CH}_2-\text{O}-\text{P}(=\text{O})(\text{CH}_3)(\text{CH}_2)_5\text{O}$		CH ₃		<5
	$\text{O}=\text{P}(=\text{O})(\text{EtO})_2$		CH ₃		7
	CO_2CH_3		CH ₃		14

Table 1 (continued)

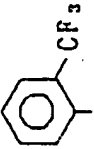
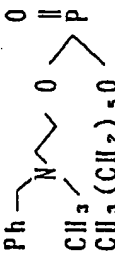
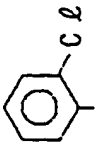
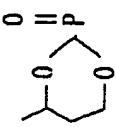
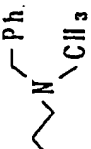
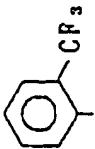
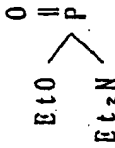
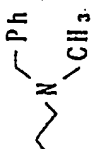
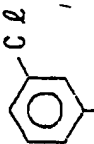
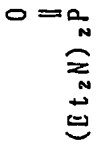
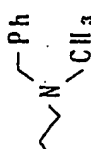
Ar ¹	Z	R ¹	R ²	R ³	IC ₅₀
		H	CH ₃	CH ₃	7
		H	CH ₃		60
		H	CH ₃		10
		H	CH ₃		21

Table 1 (continued)

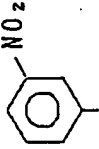
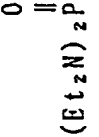
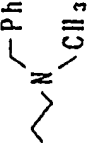
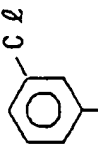
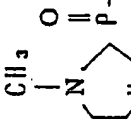
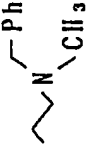
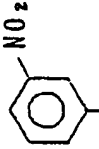
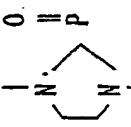
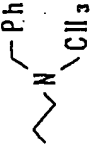
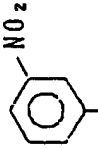
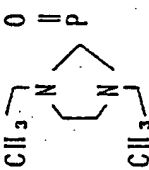
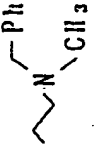
Ar ¹	Z	R ¹	R ²	R ³	IC ₅₀
		H	CH ₃		<10
		H	CH ₃		320
		H	CH ₃		300
		H	CH ₃		68

Table 1 (continued)

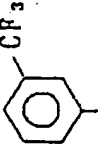

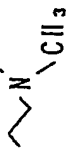
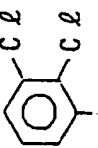
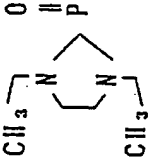
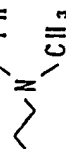
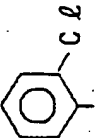
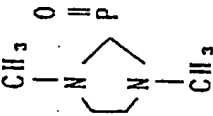
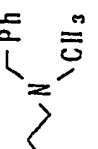
Ar ¹	Z	R ¹	R ²	R ³	IC ₅₀
		—	CH ₃		<5
		II	CH ₃		250
		II	CH ₃		32

Table 1 (continued)

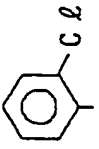
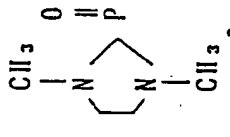
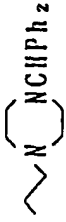
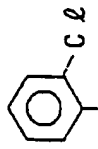
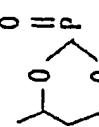
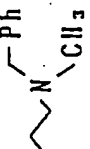
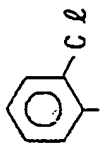
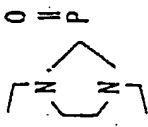
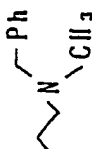
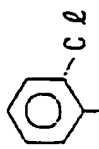
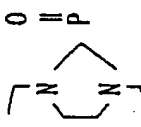
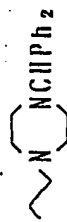
Ar ¹	Z	R ¹	R ²	R ³	IC ₅₀
		II	CH ₃		660
		—	CH ₃		52
		II	CH ₃		32
		II	CH ₃		210

Table 1 (continued)

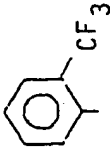
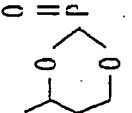
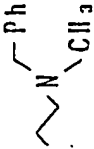
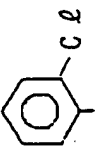
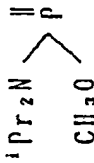
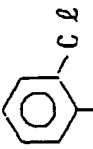
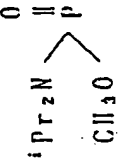
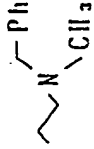
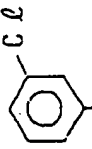
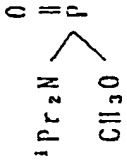
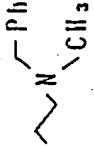
Ar ¹	Z	R ¹	R ²	R ³	IC ₅₀
		—	CH ₃		42
		H	CH ₃	Me	520
		H	CH ₃		25
		H	CH ₃		<10

Table 1 (continued)

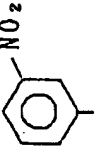
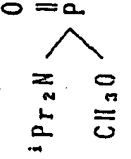

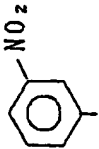
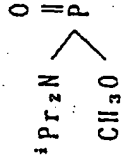
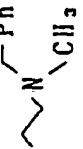
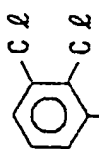
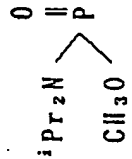
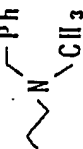
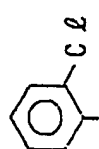
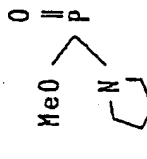
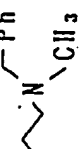
Ar ¹	Z	R ¹	R ²	R ³	IC ₅₀
		II	CH ₃		< 5
		II	CH ₃		< 10
		II	CH ₃		< 5
		II	CH ₃		52

Table 1 (continued)

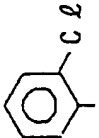
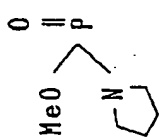
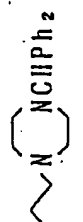
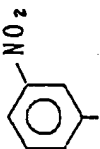
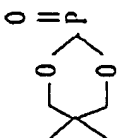

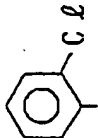

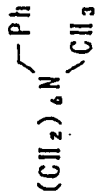
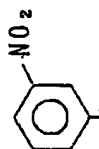
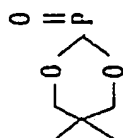
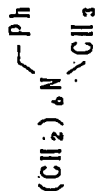
Ar ¹	Z	R ¹	R ²	R ³	IC ₅₀
		H	CH ₃		260
		H	CH ₃		5
		H	CH ₃		5
		H	CH ₃		<5

Table 1 (continued)

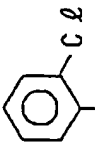
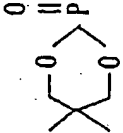
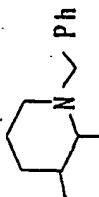
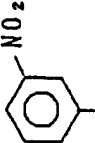
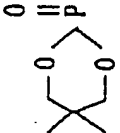
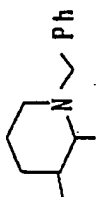
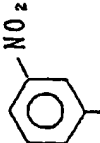
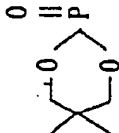

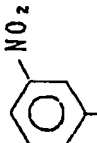
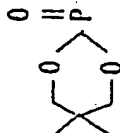
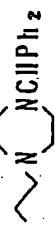
Ar ¹	Z	R ¹	R ²	R ³	IC ₅₀
		II	CH ₃		100
		II	CH ₃		<5
		II	CH ₃		500
		II	CH ₃		<5

Table 1 (continued)

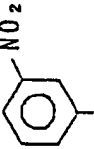
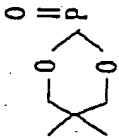
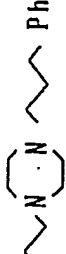
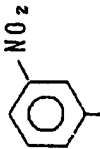

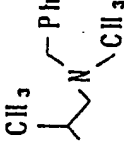
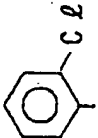
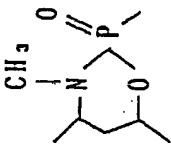

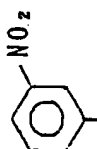
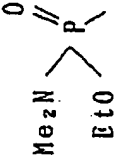
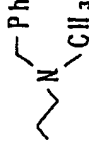
Ar ¹	Z	R ¹	R ²	R ³	IC ₅₀
		H	CH ₃		200
		H	CH ₃		260
		H	CH ₃		35
		H	CH ₃		410

Table 1 (continued)

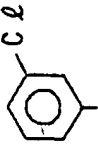
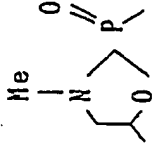

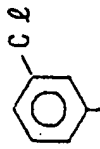
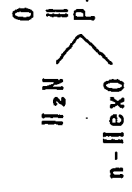
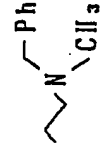
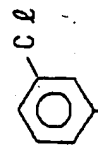
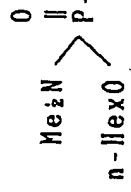
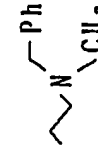
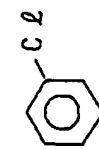
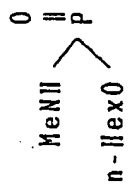
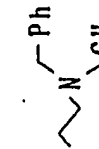
Ar ¹	Z	R ¹	R ²	R ³	IC ₅₀
		II	CH ₃		560
		II	CH ₃		300
		II	CH ₃		<10
		II	CH ₃		120

Table 1 (continued)

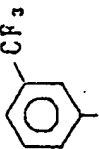
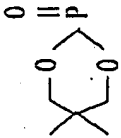

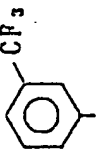
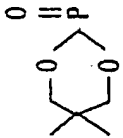
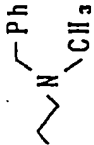
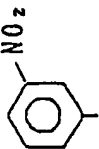
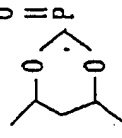

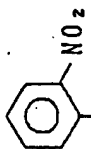
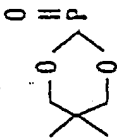

Ar ¹	Z	R ¹	R ²	R ³	IC ₅₀
		II	CH ₃		9
		II	CH ₃		41
		—	CH ₃		<5
		II	CH ₃		500

Table 1 (continued)

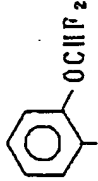
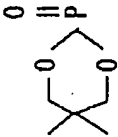
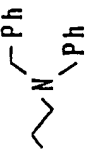
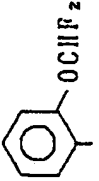
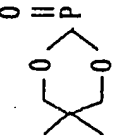

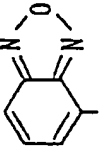
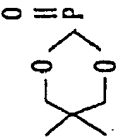
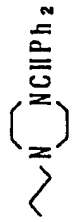
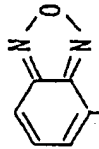
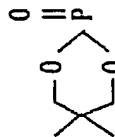
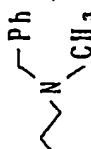
Ar ¹	Z	R ¹	R ²	R ³	IC ₅₀
		II	CH ₃		9
		II	CH ₃		6
		II	CH ₃		50
		II	CH ₃		900

Table 1 (continued)

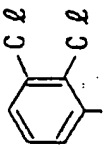
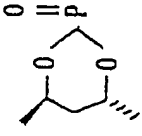
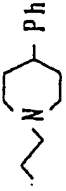
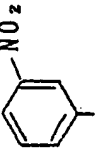
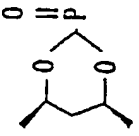

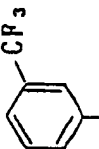
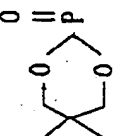
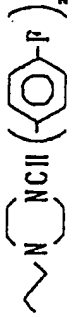
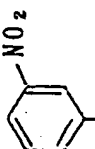
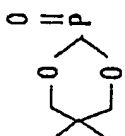

Ar ¹	Z	R ¹	R ²	R ³	IC ₅₀
		H	CH ₃		6
		H	CH ₃		<5
		H	CH ₃		8
		H	CH ₃		200

Table 1 (continued)

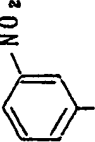
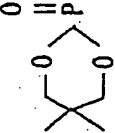

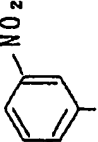

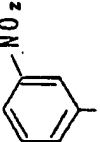
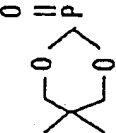
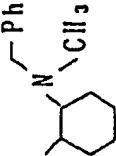
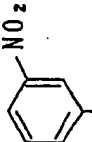
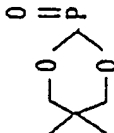
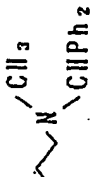
Ar ¹	Z	R ¹	R ²	R ³	IC ₅₀
		H	CH ₃		220
	CO ₂ Me	H	CH ₃		38
		H	CH ₃		130
		H	CH ₃		500

Table 1 (continued)

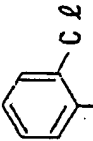
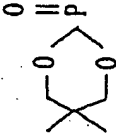

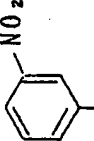


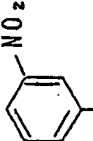
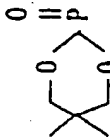

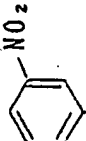
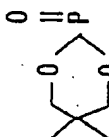

Ar ¹	Z	R ¹	R ²	R ³	IC ₅₀
		II	CH ₃		12
		II	CH ₃		5
		II	CH ₃		190
		II	CH ₃		5

Table 1 (continued)

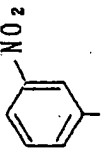
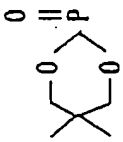
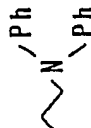
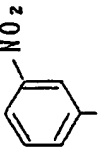
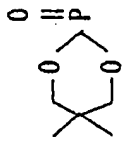

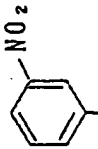
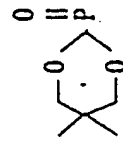
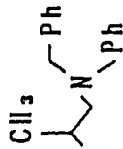
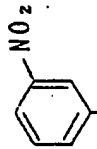
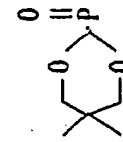
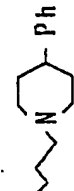
Ar ¹	Z	R ¹	R ²	R ³	IC ₅₀
		H	CH ₃		280
		H	CH ₃		6
		H	CH ₃		13
		H	CH ₃		10

Table 1 (continued)

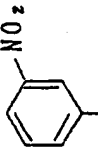
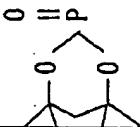
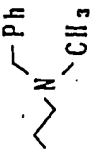
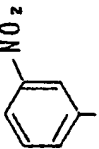
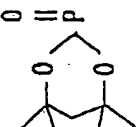
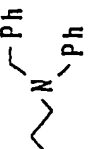
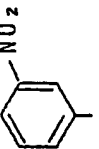
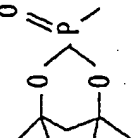
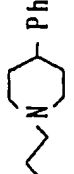
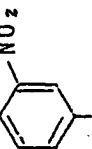
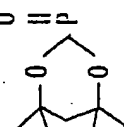
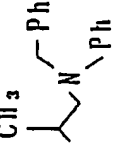
Ar ¹	Z	R ¹	R ²	R ³	IC ₅₀
		II	CH ₃		170
		II	CH ₃		20
		II	CH ₃		6
		II	CH ₃		200

Table 1 (continued)

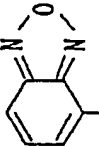
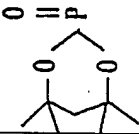
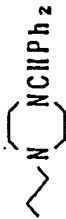
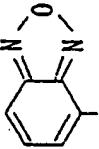
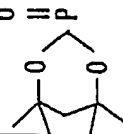
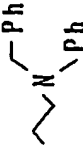
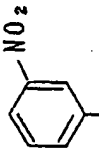
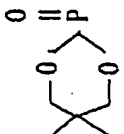

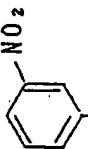
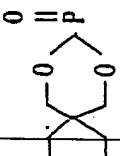

Ar ¹	Z	R ¹	R ²	R ³	IC ₅₀
		II	CH ₃		40
		II	CH ₃		28
		II	CH ₃		35
		II	CH ₃		6

Table 1 (continued)

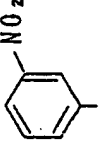
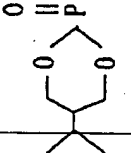

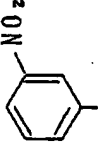
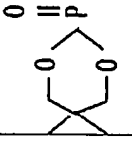
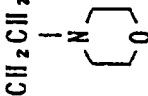
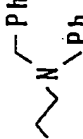
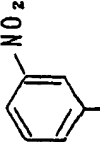
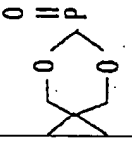

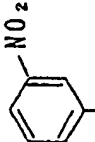
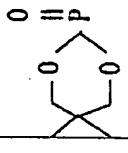

Ar ¹	Z	R ¹	R ²	R ³	IC ₅₀
		II	CH ₃		7
			CH ₃		<5
		II	CH ₃		28
		II	CH ₃		5

Table 1 (continued)

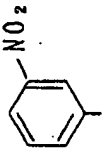
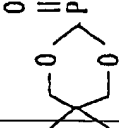
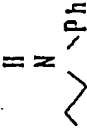
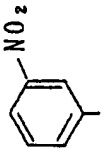
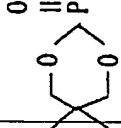
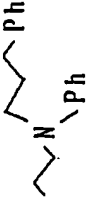
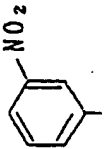
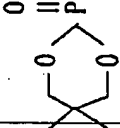
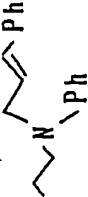
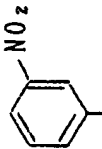
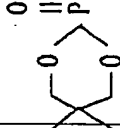
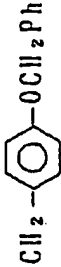
Ar ¹	Z	R ¹	R ²	R ³	IC ₅₀
		—	CH ₃		<10
		H	CH ₃		8
		H	CH ₃		500
		H	CH ₃		8

Table 1 (continued)

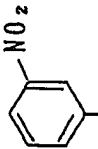
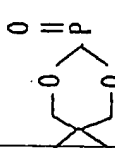
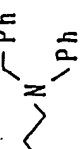
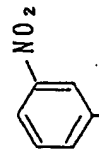
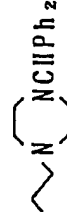
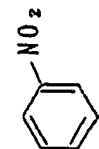
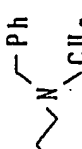
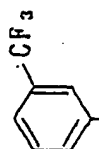
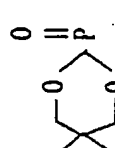
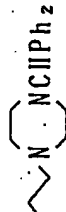
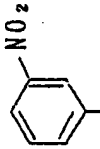

Ar ¹	Z	R ¹	R ²	R ³	IC ₅₀
		—	CH ₃		540
	CO ₂ Me	—	CH ₃		54
	CO ₂ Me	—	CH ₃		14
		—	CH ₃		6

Table 1 (continued)

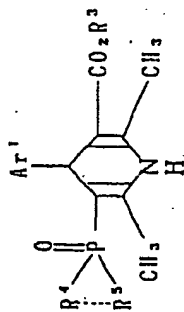
Ar ¹	Z	R ¹	R ²	R ³	IC ₅₀
	CO ₂ Me	—	CH ₃		67

TEST EXAMPLE 2

300. human carcinoma KB-3-1 cells of multidrug resistant KB-CI cells were incubated in a glucose culture medium for 16 hours. A solution of vincristine alone, or of vincristine and a sample compound in DMSO, was added thereto, and the cells were incubated at 37 °C for further 10 days. Colonies were stained with 0.5% methylene blue in 50% ethanol, and counted. The concentration of vincristine inhibiting the formation of the cell colonies 50% (IC₅₀) was investigated in the presence or absence of the sample. Each value represents relative resistance to vincristine that was determined by dividing the IC₅₀ of KB-3-1 for vincristine in the presence of a sample or the IC₅₀ of KB-CI for vincristine in the absence of the sample by the IC₅₀ of KB-3-1 for vincristine in the absence of the sample

The test results are shown in Table 2.

Table 2: Activities for enhancing drug effects of vincristine against parent strain (KB-3-1) and its drug resistant strain (KB-Cl)



(In the Table, Ph means phenyl.)

Compound No.	Ar ¹	R ³	R ⁴ --- R ⁵	Concentration (µg/m ²)	KB-3-1	KB-Cl
	No administration			0	1	1200
(1)	m-Nitrophenyl	CH ₂ CH ₂ N(CH ₃)CH ₂ Ph	OCH ₂ C(CH ₃) ₂ CH ₂ O	10	0.2	34
(2)	m-Nitrophenyl	2-(4-diphenylmethyl-1-piperazinyl)ethyl	OCH(CH ₃)CH ₂ CH(CH ₃)O	10	0.1	0.5
(3)	m-Nitrophenyl	CH ₂ CH ₂ N(CH ₃)CH ₂ Ph	R ⁴ : CH ₃ O R ⁵ : CH ₃ O	10	0.2	14
(4)	m-Nitrophenyl	CH ₃	R ⁴ : PhCH ₂ N(CH ₃)(CH ₂) ₃ O R ⁵ : CH ₃ O	10	0.1	18
(5)	m-Nitrophenyl	CH ₂ CH ₂ N(CH ₃)CH ₂ Ph	R ⁴ : (CH ₃) ₂ N R ⁵ : C ₂ H ₅ O	10	0.1	0.7
(6)	m-Chlorophenyl	CH ₂ CH ₂ N(CH ₃)CH ₂ Ph	N(CH ₃)CH ₂ CH ₂ N(CH ₃)	10	0.1	1.0

Now, two typical methods for oxidizing 1,4-dihydropyridine derivatives to the corresponding pyridine derivatives, will be described in detail.

OXIDATION EXAMPLE 1

Preparation of 5-(cis-4,6-dimethyl-1,3,2-dioxaphosphorinan-2-yl)-2, dimethyl-4-(3-nitrophenyl)-3-pyridinecarboxylic acid 4-diphenylmethyl-1-piperadinoethylester p-oxide

10 ml of 36% nitric acid was added to 1.4 g of 5-(cis-4,6-dimethyl-1,3,2-dioxaphosphorinan-2-yl)-1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3-pyridinecarboxylic acid 4-diphenylmethyl-1-piperadinoethylester p-oxide dihydrochloride, and the mixture was stirred at 50 °C for 10 minutes.

After cooling, the mixture was neutralized with a saturated sodium hydrogencarbonate aqueous solution and extracted with chloroform. The extract was dried over anhydrous sodium sulfate. Then, the solvent was distilled off under reduced pressure, and the residue was subjected to silica gel chromatography (developing solvent: ethyl acetate R_f = 0.5) to obtain 1.2 g (yield 95%) of the above identified compound as yellow oily substance.

The analytical values are shown below.

NMR δ (ppm) $CDCl_3$

1.02(3H,dd,J=1.6Hz,6.2Hz), 1.16(3H,dd,J=1.6Hz,6.2Hz), 1.12(1H,m), 1.57(1H,m), 2.20-2.50(10H,m), 2.59(3H,s), 2.99(3H,s), 3.90-4.10(2H,m), 4.19(1H,s), 4.60-4.80(2H,m), 7.17(2H,t,J=7.4Hz), 7.26(4H,dd,J=7.4Hz,7.0Hz), 7.39(4H,d,J=7.0Hz), 7.53(1H,m), 7.59(1H,m), 8.15(1H,m), 8.25(1H,m)

MS(FAB) 699 (50%, M + 1),

167 (100%)

OXIDATION EXAMPLE 2

Preparation of 5-(5,5-dimethyl-1,3,2-dioxaphosphorinan-2-yl)-2,6-dimethyl-4-(3-nitrophenyl)-3-pyridinecarboxylic acid 2-(N-phenyl)aminoethylester p-oxide

5.6 g of 5-(5,5-dimethyl-1,3,2-dioxaphosphorinan-2-yl)-1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3-pyridinecarboxylic acid 2-(N-phenyl)aminoethylester p-oxide was dissolved in 20 ml of acetic acid. After adding 2 g of chromium trioxide, the mixture was heated at 100 °C for 30 minutes.

After cooling, the solvent was distilled off under reduced pressure. To the residue, a saturated sodium hydrogencarbonate aqueous solution was added for neutralization, and the mixture was extracted with 100 ml of ethyl acetate. The extract was dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. To the residue, 10 ml of methanol, 10 ml of ethanol and 2 g of p-toluene sulfonic acid, and the mixture was refluxed under heating for 7 hours. The solvent was distilled off under reduced pressure. Then, a saturated sodium hydrogencarbonate aqueous solution was added, and the mixture was extracted with 100 ml of ethyl acetate. The extract was dried over anhydrous sodium sulfate. Then, solvent was distilled off under reduced pressure, and the residue was subjected to silica gel chromatography (developing solvent: ethyl acetate R_f = 0.6) to obtain 4.2 g of the above-identified compound (yield: 79%, melting point: 105 - 106 °C) as yellow crystals.

The analytical values are shown below.

NMR δ (ppm) $CDCl_3$

0.75(3H,s), 1.09(3H,s), 2.60(3H,s), 2.89(3H,s), 3.0-3.70(6H,m), 4.14(2H,t,J=6Hz), 6.30-8.30(9H,m)

Now, examples for the drugs containing the compounds of the present invention will be presented.

EXAMPLES 1: Hard capsules for oral administration

25 g of hydrochloride of the compound (2), 5 g of adriamycin and 7.5 g of polyoxyethylene castor oil were dissolved in methanol. Then, 25 g of silicic anhydride was mixed thereto. Methanol was distilled off, and then 5 g of calcium carboxymethyl cellulose, 5 g of corn starch, 7.5 g of hydroxypropyl cellulose and 20 g of fine crystal cellulose were mixed thereto. Then, 30 ml of water was added, and the mixture was kneaded and granulated. The product was granulated by a granulation machine equipped with a screen of No. 24 mesh (B.S.). Granules were dried to a water content of not higher than 5% and sieved with a screen of No. 16 mesh (B.S.). Then, the particles were filled in capsules by a capsule filling machine in an amount of 200 mg per capsule.

EXAMPLE 2: Soft capsules for oral administration

30 g of hydrochloride of compound (2), 7.5 g of adriamycin and 130 g of polyethylene glycol (Macrogol 400) were mixed to obtain a uniform solution.

Separately, a gelatin solution comprising 93 g of gelatin, 19 g of glycerol, 10 g of D-sorbitol, 0.4 g of ethyl p-oxybenzoate, 0.2 g of propyl p-oxybenzoate and 0.4 g of titanium oxide, was prepared. By using this as a capsule coating agent, soft capsules each containing 190 mg of the content were prepared by a manual flat plate punching method.

EXAMPLE 3: Soft capsules for oral administration.

40 g of hydrochloride of compound (2), 4 g of adriamycin and 120 g of polyethylene glycol (Macrogol 400) were mixed to obtain a uniform solution.

Separately, a gelatin solution comprising 90 g of gelatin, 16 g of glycerol, 8 g of D-sorbitol, 0.35 g of ethyl p-oxybenzoate, 0.2 g of propyl p-oxybenzoate and 0.3 g of titanium oxide, was prepared. By using this as a capsule coating agent, soft capsules each containing 180 mg of the content were prepared by a manual flat plate punching method.

EXAMPLE 4: Injection drug

1 g of hydrochloride of compound (2), 1 g of adriamycin, a suitable amount of peanut oil and 1 g of benzyl alcohol were mixed, and the total amount was brought to 100 ml by using peanut oil. The solution thus obtained was put into ampules in an amount of 1 ml under an aseptic condition and the ampules were closed.

EXAMPLE 5: Injection drug

1 g of hydrochloride of compound (2), 1 g of adriamycin, 5.0 g of hydrogenated castor oil polyoxyethylene (60 mol) ether (Nikkol HCO 60, tradename), 20 g of propylene glycol, 10 g of glycerol and 5.0 g of ethyl alcohol were mixed, and 100 ml of distilled water was added thereto. The mixture was stirred to obtain a solution. The solution was put into ampules in an amount of 2.0 ml each under an aseptic condition, and the ampules were then closed.

EXAMPLE 6: Injection drug

1 g of hydrochloride of compound (2), 1 g of adriamycin, 5.0 g of hydrogenated castor oil polyoxyethylene (60 mol) ether (Nikkol HCO 60, tradename), 20 g of propylene glycol, 10 g of glycerol and 5.0 g of ethyl alcohol were mixed, and 100 ml of distilled water was added thereto. The mixture was stirred to obtain a solution. This solution was put into ampules in an amount of 2.0 ml each under an aseptic condition, and the ampules were closed.

EXAMPLE 7: Hard capsules for oral administration.

25 g of hydrochloride of compound (2), 5 g of vincristine and 7.5 g of polyoxyethylene castor oil were dissolved in methanol. Then, 25 g of silicic anhydride was added thereto, methanol was evaporated, and 5 g of calcium carboxymethyl cellulose, 5 g of corn starch, 7.5 g of hydroxypropyl cellulose and 20 g of fine crystalline cellulose were mixed, and 30 ml of water was added thereto. The mixture was kneaded and granulated. This product was granulated by a granulator with a screen of No. 24 mesh (B.S.). Granules thus obtained were dried to a water content of not higher 5% and then sieved with a screen with No. 16 mesh (B.S.).

Then, the particles thus obtained were filled into capsules by a capsule filling machine in an amount of 200 mg per capsule.

EXAMPLE 8: Soft capsules for oral administration

30 g of hydrochloride of compound (2), 7.5 of vincristine and 130 g of polyethylene glycol (Macrogol 400) were mixed to obtain a uniform solution.

Separately, a gelatin solution comprising 93 g of gelatin, 19 g of glycerol, 10 g of D-sorbitol, 0.4 g of ethyl p-oxybenzoate, 0.2 g of propyl p oxybenzoate and 0.4 g of titanium oxide, was prepared. By using this as a capsule coating agent, soft capsules containing 190 mg of the content were prepared by a manual flat plate punching method.

EXAMPLE 9: Soft capsules for oral administration

40 g of hydrochloride of compound (2), 4 g of vincristine and 120 g of polyethylene glycol (Macrogol 400) were mixed to obtain a uniform solution.

Separately, a gelatin solution comprising 90 g of gelatin, 16 g of glycerol, 8 g of D-sorbitol, 0.35 g of ethyl p-oxybenzoate, 0.2 g of propyl p-oxybenzoate and 0.3 g of titanium oxide, was prepared. By using this as a capsule coating agent, soft capsules containing 180 mg of the content were prepared by a manual flat plate punching method.

EXAMPLE 10: Injection drug

1 g of hydrochloride of compound (2), 1 g of vincristine, a suitable amount of peanut oil and 1 g of benzyl alcohol were mixed, and the total amount was brought to 100 cc by using peanut oil. This solution was put into ampules in an amount of 1 ml per ampule under an aseptic condition, and the ampules were closed.

EXAMPLE 11: Injection drug

1 g of hydrochloride of compound (2), 1 g of vincristine, 5.0 g of hydrogenated castor oil polyoxyethylene (60 mol) ether (Nikkol HCO 60, tradename), 20 g of propylene glycol, 10 g of glycerol and 5.0 g of ethyl alcohol were mixed, and 100 ml of distilled water was added thereto. The mixture was stirred to obtain a solution. This solution was put into ampules in an amount of 2.0 ml per ampule under an aseptic condition, and the ampules were closed.

EXAMPLE 12: Injection drug

1 g of hydrochloride of compound (2), 1 g of vincristine, 5.0 g of hydrogenated castor oil polyoxyethylene (60 mol) ether (Nikkol HCO 60, tradename), 20 g of propylene glycol, 10 g of glycerol and 5.0 g of ethyl alcohol were mixed, and 100 ml of distilled water was added thereto. The mixture was stirred to obtain a solution. This solution was put into ampules in an amount of 2.0 ml per ampule under an aseptic condition, and the ampules were closed.

Now, Examples will be given to illustrate the preparation of a drug in which the compound of the present invention is administered separately from an antitumor drug.

EXAMPLE 13: Tablets

Composition (1,000 tablets)

Hydrochloride of the compound of Example (2)	55.0 (g)
Lactose	190.0
Corn starch	75.0
Fine crystalline cellulose	25.0
Methyl cellulose	3.0
Magnesium stearate	2.0
	350.0 (g)

The above components were charged into a V-type mixer and uniformly mixed. This powder mixture was directly tableted to obtain tablets having a weight of 350 mg per tablet.

EXAMPLE 14: Capsules

Composition (1,000 capsules)

Hydrochloride of the compound of Example (2)	55 (g)
Corn starch	145
Fine crystalline cellulose	145
Magnesium stearate	5
	350 (g)

The above compositions were charged into a V-type mixer and uniformly mixed. This powder mixture was filled in hard capsules. The content per capsule was 350 mg.

EXAMPLE 15: Syrups

Composition (2% solution)

Hydrochloride of the compound of Example (2)	2.0 (g)
Sucrose	30.0
Glycerol	5.0
Flavor	0.1
96% Ethanol	10.0
Methyl p-oxybenzoate	0.03
Distilled water to bring the total amount to 100.0 g	

Sucrose and hydrochloride of the compound of Example 1 were dissolved in 60 g of warm water and then cooled. Thereafter, a flavor solution dissolved in glycerol and ethanol was added thereto. Then, water was added to this mixture to bring the total amount to 100.0 g.

EXAMPLE 16: Powder

Hydrochloride of the compound of Example (2)	5.0 (g)
Lactose	84.0
Fine crystalline cellulose	10.0
Methyl cellulose	1.0
	100.0 (g)

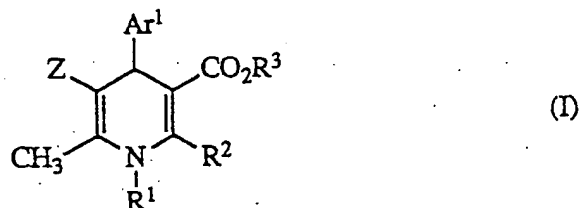
The above components were charged into a V-type mixer and uniformly mixed.

EXAMPLE 17: Injection drug

1 g of hydrochloride of compound (2), a suitable amount of peanut oil and 1 g of benzyl alcohol were mixed, and the total amount was brought to 100 cc by using peanut oil. This solution was put into ampules in an amount of 1 ml per ampule under an aseptic condition, and the ampules were closed.

Claims

1. Use of a compound of the formula I:



15 wherein Ar¹ is phenyl, pyridyl, furyl, or 2,1,3-benzooxadiazol-4-yl, which may be substituted by one or two substituents selected from the group consisting of NO₂, CF₃, Br, Cl, F, R⁶ (wherein R⁶ is C₁-C₄ alkyl), OH, OR⁵, OCHF₂, COOR⁶, NH₂, NHR⁶, NR⁶R⁷ (wherein R⁷ has the same meaning as R⁶), CONH₂, CONHR⁶, CONR⁶R⁷, COSR⁶, SR⁶, S(O)R⁶, S(O)₂R⁶, SO₃H, SO₃R⁶, SO₂NH₂, SO₂NHR⁶, SO₂NR⁶R⁷, CN and phenyloxy;

20 Z is a group of the formula II:



30 wherein each of R⁴ and R⁵ which may be the same or different is OH, C₁-C₁₂ linear or branched primary or secondary alkyloxy, C₃-C₆ linear or branched alkenyloxy or alkynyloxy, C₃-C₆ cycloalkyloxy, C₁-C₆ alkoxy substituted by C₃-C₆ cycloalkyl, OAr² (wherein Ar² is phenyl which may be substituted by halogen, C₁-C₃ alkyl or C₁-C₃ alkoxy), OANR⁶R⁷ (wherein A is C₂-C₆ alkylene, which may be substituted by C₁-C₃ alkyl or Ar²), OAN(CH₂Ar²)R⁶, OAR⁶, OACN, NH₂, NHR⁶, NR⁶R⁷, 1-piperidinyl or 1-pyrrolidinyl, or R⁴ and R⁵ together form OYO (wherein Y is C₂-C₄ linear alkylene which may be substituted by R⁶, CO₂R⁶, OR⁶ or A), NHYO, R⁶NYO, NHYNH, R⁶NYNH or R⁶NYNR⁷;

R¹ is hydrogen, R⁶, ANR⁶R⁷, AN(CH₂CH₂)₂O, AOR⁶ or CH₂phenyl;

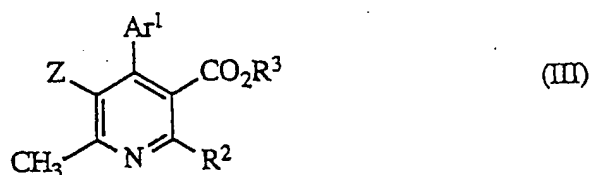
35 R² is R⁶, Ar², Ar²CH=CH, Ar²CH(OH)CH₂, CHO, CN, CH₂OH, CH₂OR⁶, CH₂CH₂N(CH₂CH₂)₂NR⁶, NH₂, NHR⁶ or NR⁶R⁷;

40 R³ is hydrogen, C₁-C₁₂ linear or branched alkyl, C₃-C₆ linear or branched alkenyl or alkynyl, C₃-C₆ cycloalkyl, C₁-C₆ alkyl substituted by C₃-C₆ cycloalkyl, AOR⁶, AO(CH₂)_mAr², (wherein m is an integer of from 0 to 3), (CH₂)_mAr², ANH₂, ANHR⁶, ANR⁶R⁷, ANR⁶(CH₂)_mAr², AN{(CH₂)_mAr²}{(CH₂)_nAr³} (wherein n has the same meaning as m, and Ar³ has the same meaning as Ar²), the 1-benzyl-4-piperidinyl, 1-benzyl-2-piperidinyl, 2-pyridinylmethyl, 3-pyridinylmethyl, AQ (wherein Q is pyrrolidine or piperidine which may be substituted by (CH₂)_mAr²), 4-R⁶-1-piperazinyl, 4-Ar²-1-piperazinyl, 4-(Ar²)₂CH-1-piperazinyl or 4-(Ar²)₂CH-1-(1,4-diazacycloheptyl);

45 or a pharmaceutically acceptable salt of the compound, for the manufacture of an agent for enhancing the drug effect of an anti-tumor drug.

2. The use according to Claim 1, wherein any one of the substituents R¹, R², R³, R⁴ and R⁵ in the compound of the formula I contains at least one basic nitrogen atom capable of forming a salt.

- 50 3. Use of a compound of the formula III:



wherein Ar¹ is phenyl, pyridyl, furyl, or 2,1,3-benzooxadiazol-4-yl, which may be substituted by one or two substituents selected from the group consisting of NO₂, CF₃, Br, Cl, F, R⁶ (wherein R⁶ is C₁-C₄ alkyl), OH, OR⁶, OCHF₂, COOR⁶, NH₂, NHR⁶, NR⁶R⁷ (wherein R⁷ has the same meaning as R⁶), CONH₂, CONHR⁶, CONR⁶R⁷, COSR⁶, SR⁶, S(O)R⁶, S(O)₂R⁶, SO₃H, SO₃R⁶, SO₂NH₂, SO₂NHR⁶, SO₂NR⁶R⁷, CN and phenyloxy;

Z is a group of the formula II:



wherein each of R⁴ and R⁵ which may be the same or different is OH, C₁-C₁₂ linear or branched primary or secondary alkyloxy, C₃-C₆ linear or branched alkenyloxy or alkynyloxy, C₃-C₆ cycloalkyloxy, C₁-C₆ alkoxy substituted by C₃-C₆ cycloalkyl, OAr² (wherein Ar² is phenyl which may be substituted by halogen, C₁-C₃ alkyl or C₁-C₃ alkoxy), OANR⁶R⁷ (wherein A is C₂-C₆ alkylene, which may be substituted by C₁-C₃ alkyl or Ar²), OAN(CH₂Ar²)R⁶, OAOR⁶, OACN, NH₂, NHR⁶, NR⁶R⁷, 1-piperidinyl or 1-pyrrolidinyl, or R⁴ and R⁵ together form OYO (wherein Y is C₂-C₄ linear alkylene which may be substituted by R⁶, CO₂R⁶, OR⁶ or A), NHYO, R⁶NYO, NHYNH, R⁶NYNH or R⁶NYNR⁷, or Z is CO₂R⁸ - (wherein R⁸ has the same meaning as R³ defined hereinafter);

R² is R⁶, Ar², Ar²CH=CH, Ar²CH(OH)CH₂, CHO, CN, CH₂OH, CH₂OR⁶, CH₂CH₂N(CH₂CH₂)₂NR⁶, NH₂, NHR⁶ or NR⁶R⁷;

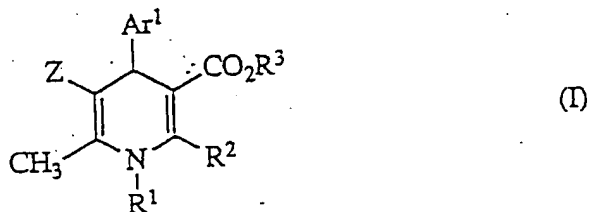
R³ is hydrogen, C₁-C₁₂ linear or branched alkyl, C₃-C₆ linear or branched alkenyl or alkynyl, C₃-C₆ cycloalkyl, C₁-C₆ alkyl substituted by C₃-C₆ cycloalkyl, AOR⁶, AO(CH₂)_mAr², (wherein m is an integer of from 0 to 3), (CH₂)_mAr², ANH₂, ANHR⁶, ANR⁶R⁷, ANR⁶(CH₂)_mAr², {AN(CH₂)_mAr²}{(CH₂)_nAr³} (wherein n has the same meaning as m, and Ar³ has the same meaning as Ar²), the 1-benzyl-4-piperidinyl, 1-benzyl-2-piperidinyl, 2-pyridinylmethyl, 3-pyridinylmethyl, AQ (wherein Q is pyrrolidine or piperidine which may be substituted by (CH₂)_mAr²), 4-R⁶-1-piperazinyl, 4-Ar²-1-piperazinyl, 4-(Ar²)₂CH-1-piperazinyl or 4-(Ar²)₂CH-1-(1,4-diazacycloheptyl);

or a pharmaceutically acceptable salt of the compound for the manufacture of an agent for enhancing the drug effect for an anti-tumor drug.

4. Use according to Claim 3, wherein any one of the substituents R¹, R², R³, R⁴ and R⁵ in the compound of the formula I contains at least one basic nitrogen atom capable of forming a salt.

Patentansprüche

1. Verwendung einer Verbindung der Formel I:



worin Ar¹ Phenyl, Pyridyl, Furyl oder 2,1,3-Benzooxadiazol-4-yl, das substituiert sein kann durch ein oder zwei Substituenten, ausgewählt aus der Gruppe, bestehend aus NO₂, CF₃, Br, Cl, F, R⁶ (wobei R⁶ C₁-C₄-Alkyl ist), OH, OR⁶, OCHF₂, COOR⁶, NH₂, NHR⁶, NR⁶R⁷ (wobei R⁷ dieselbe Bedeutung wie R⁶ hat), CONH₂, CONHR⁶, CONR⁶R⁷, COSR⁶, SR⁶, S(O)R⁶, S(O)₂R⁶, SO₃H, SO₃R⁶, SO₂NH₂, SO₂NHR⁶, SO₂NR⁶R⁷, CN und Phenyloxy, ist;

Z eine Gruppe der Formel II ist:



5

wobei R^4 und R^5 , die gleich oder verschieden sein können, jeweils OH, C_1 - C_{12} lineares oder verzweigtes primäres oder sekundäres Alkyloxy, C_3 - C_6 lineares oder verzweigtes Alkenyloxy oder Alkynyloxy, C_3 - C_6 -Cycloalkyloxy, C_1 - C_6 -Alkoxy, substituiert durch C_3 - C_6 -Cycloalkyl, OAr^2 (wobei Ar^2 Phenyl ist, das substituiert sein kann durch Halogen, C_1 - C_3 -Alkyl oder C_1 - C_3 -Alkoxy), OANR^6R^7 (wobei A C_2 - C_6 -Alkyl ist, das substituiert sein kann durch C_1 - C_3 -Alkyl oder Ar^2), $\text{OAN}(\text{CH}_2\text{Ar}^2)\text{R}^6$, OAOR^6 , OACN , NH_2 , NHR^6 , NR^6R^7 , 1-Piperidinyll oder 1-Pyrrolidinyll ist, oder R^4 und R^5 zusammen OYO bilden (worin Y C_2 - C_4 -lineares Alkyl ist, das substituiert sein kann durch R^6 , CO_2R^6 , OR^6 oder A), NHYO , R^6NYO , NHYNH , R^6NYNH oder R^6NYNR^7 ;

15

R^1 Wasserstoff, R^6 , ANR^6R^7 , $\text{AN}(\text{CH}_2\text{CH}_2)_2\text{O}$, AOR^6 oder CH_2phenyl ist;

R^2 R^6 , Ar^2 , $\text{Ar}^2\text{CH}=\text{CH}$, $\text{Ar}^2\text{CH}(\text{OH})\text{CH}_2$, CHO , CN , CH_2OH , CH_2OR^6 , $\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)_2\text{NR}^6$, NH_2 , NHR^6 oder NR^6R^7 ist;

20

R^3 Wasserstoff, C_1 - C_{12} lineares oder verzweigtes Alkyl, C_3 - C_6 lineares oder verzweigtes ungesättigtes Alkenyl oder Alkynyl, C_3 - C_6 -Cycloalkyl, C_1 - C_6 -Alkyl, substituiert durch C_3 - C_6 -Cycloalkyl, AOR^6 , $\text{AO}(\text{CH}_2)_m\text{Ar}^2$ (wobei m eine ganze Zahl von 0 bis 3 ist), $(\text{CH}_2)_m\text{Ar}^2$, ANH_2 , ANHR^6 , ANR^6R^7 , $\text{ANR}^6(\text{CH}_2)_m\text{Ar}^2$, $\text{AN}\{(\text{CH}_2)_m\text{Ar}^2\}\{(\text{CH}_2)_n\text{Ar}^3\}$ (wobei n dieselbe Bedeutung hat wie m, und Ar^3 dieselbe Bedeutung hat wie Ar^2), 1-Benzyl-4-piperidinyll, 1-Benzyl-2-piperidinyll, 2-Pyridinylmethyl, 3-Pyridinylmethyl, AQ (wobei Q Pyrrolidin oder Piperidin ist, das substituiert sein kann durch $(\text{CH}_2)_m\text{Ar}^2$), 4- R^6 -1-Piperazinyll, 4- Ar^2 -1-Piperazinyll, 4- $(\text{Ar}^2)_2\text{CH}$ -1-Piperazinyll oder 4- $(\text{Ar}^2)_2\text{CH}$ -1-(1,4-Diazacycloheptyll) ist; oder ein pharmazeutisch verträgliches Salz der Verbindung zur Herstellung eines Mittels zur Verbesserung der Arzneimittelwirkung eines Antitumormittels.

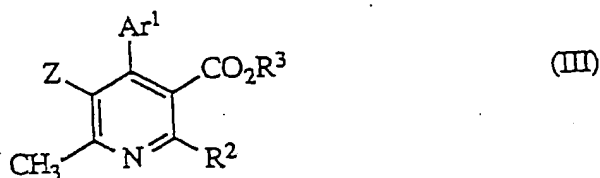
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2. Verwendung gemäß Anspruch 1, wobei irgendeiner der Substituenten R^1 , R^2 , R^3 , R^4 und R^5 in der Verbindung der Formel I mindestens ein basisches Stickstoffatom enthält, das fähig ist, ein Salz zu bilden.

30

3. Verwendung einer Verbindung der Formel III:

35



40

wobei Ar^1 Phenyl, Pyridyl, Furyl oder 2,1,3-Benzooxadiazol-4-yl ist, das substituiert sein kann durch ein oder zwei Substituenten, ausgewählt aus der Gruppe, bestehend aus NO_2 , CF_3 , Br, Cl, F, R^6 (wobei R^6 C_1 - C_4 -Alkyl ist), OH, OR^6 , OCHF_2 , COOR^6 , NH_2 , NHR^6 , NR^6R^7 (wobei R^7 dieselbe Bedeutung wie R^6 hat), CONH_2 , CONHR^6 , CONR^6R^7 , COSR^6 , SR^6 , $\text{S}(\text{O})\text{R}^6$, $\text{S}(\text{O})_2\text{R}^6$, SO_3H , SO_3R^6 , SO_2NH_2 , SO_2NHR^6 , $\text{SO}_2\text{NR}^6\text{R}^7$, CN und Phenyloxy;

45

Z ist eine Gruppe der Formel II:

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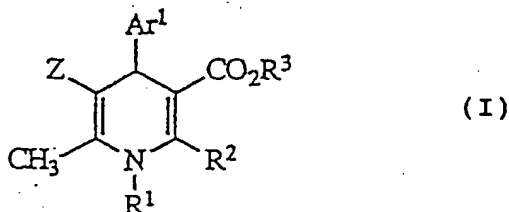
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wobei R^4 und R^5 , die jeweils gleich oder verschieden sein können, jeweils OH, C_1 - C_{12} lineares oder verzweigtes primäres oder sekundäres Alkyloxy, C_3 - C_6 lineares oder verzweigtes Alkenyloxy oder

- Alkynyloxy, C₃-C₆-Cycloalkyloxy, C₁-C₆-Alkoxy, substitué par C₃-C₆-Cycloalkyl, OAr² (wobei Ar² Phenyl ist, das substituiert sein kann durch Halogen, C₁-C₃-Alkyl oder C₁-C₃-Alkoxy), OANR⁶R⁷ (wobei A C₂-C₆-Alkyl ist, das substituiert sein kann durch C₁-C₃-Alkyl oder Ar²), OAN(CH₂Ar²)R⁶, OAOR⁶, OACN, NH₂, NHR⁶, NR⁶R⁷, 1-Piperidinyloxy oder 1-Pyrrolidinyloxy ist, oder R⁴ und R⁵ zusammen OYO bilden (worin Y C₂-C₄-lineares Alkyl ist, das substituiert sein kann durch R⁶, CO₂R⁶, OR⁶ oder A), NHYO, R⁶NYO, NHYNH, R⁶NYNH oder R⁶NYNR⁷, oder Z ist CO₂R⁸ (worin R⁸ dieselbe Bedeutung wie R³, wie hiernach definiert, hat);
- R² ist R⁶, Ar², Ar²CH=CH, Ar²CH(OH)CH₂, CHO, CN, CH₂OH, CH₂OR⁶, CH₂CH₂N(CH₂CH₂)₂NR⁶, NH₂, NHR⁶ oder NR⁶R⁷;
- R³ ist Wasserstoff, C₁-C₁₂ lineares oder verzweigtes Alkyl, C₃-C₆ lineares oder verzweigtes Alkenyl oder Alkynyl, C₃-C₆-Cycloalkyl, C₁-C₆-Alkyl, substituiert durch C₃-C₆-Cycloalkyl, AOR⁶, AO(CH₂)_mAr² (wobei m eine ganze Zahl von 0 bis 3 ist), (CH₂)_mAr², ANH₂, ANHR⁶, ANR⁶R⁷, ANR⁶(CH₂)_mAr², AN{(CH₂)_mAr²}{(CH₂)_nAr³} (wobei n dieselbe Bedeutung hat wie m, und Ar³ dieselbe Bedeutung hat wie Ar²), 1-Benzyl-4-piperidinyloxy, 1-Benzyl-2-piperidinyloxy, 2-Pyridinylmethyl, 3-Pyridinylmethyl, AQ (wobei Q Pyrrolidin oder Piperidin ist, das substituiert sein kann durch (CH₂)_mAr²), 4-R⁶-1-Piperazinyl, 4-Ar²-1-Piperazinyl, 4-(Ar²)₂CH-1-Piperazinyl oder 4-(Ar²)₂CH-1-(1,4-Diazacycloheptyl); oder ein pharmazeutisch verträgliches Salz der Verbindung zur Herstellung eines Mittels zur Verbesserung der Arzneimittelwirkung eines Antitumormittels.
4. Verwendung gemäß Anspruch 3, wobei irgendeiner der Substituenten R¹, R², R³, R⁴ und R⁵ in der Verbindung der Formel I mindestens ein basisches Stickstoffatom enthält, das fähig ist, ein Salz zu bilden.

Revendications

1. Utilisation d'un composé de la formule (I):



dans laquelle :

- Ar¹ représente phényle, pyridyle, furyle ou 2,1,3-benzooxadiazol-4-yle, qui peut être substitué par un ou deux substituants choisis dans le groupe constitué par : NO₂, CF₃, Br, Cl, F, R⁶ (où R⁶ représente alkyle en C₁-C₄), OH, OR⁶, OCHF₂, COOR⁶, NH₂, NHR⁶, NR⁶R⁷ (où R⁷ a la même signification que R⁶), CONH₂, CONHR⁶, CONR⁶R⁷, COSR⁶, SR⁶, S(O)R⁶, S(O)₂R⁶, SO₃H, SO₃R⁶, SO₂NH₂, SO₂NHR⁶, SO₂NR⁶R⁷, CN et phényloxy ;
- Z représente un groupe de la formule (II) :



dans laquelle R⁴ et R⁵, qui peuvent être identiques ou différents, représentent chacun OH, alkyloxy, primaire ou secondaire, linéaire ou ramifié, en C₁-C₁₂, alcényloxy ou alcynyloxy linéaire ou ramifié en C₃-C₆, cycloalkyloxy en C₃-C₆, alkoxy en C₁-C₆ substitué par cycloalkyle en C₃-C₆, OAr² (où Ar² représente phényle qui peut être substitué par halogène, alkyle en C₁-C₃ ou alkoxy en C₁-C₃), OANR⁶R⁷ (où A représente alkylène en C₂-C₆, qui peut être substitué par alkyle en C₁-C₃ ou Ar²), OAN(CH₂Ar²)R⁶, OAOR⁶, OACN, NH₂, NHR⁶, NR⁶R⁷, 1-pipéridinyloxy ou 1-pyrrolidinyloxy, ou bien

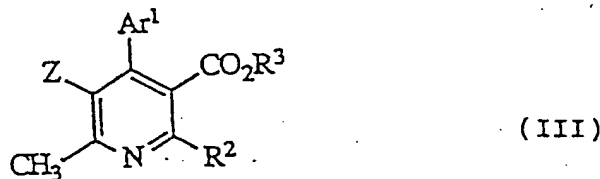
R⁴ et R⁵ forment ensemble OYO (où Y représente alkylène linéaire en C₂-C₄ qui peut être substitué par R⁶, CO₂R⁶, OR⁶ ou A), NHYO, R⁶ NYO, NHYNH, R⁶ NYNH, ou R⁶ NYNR⁷ ;

- R¹ représente hydrogène, R⁶, ANR⁶R⁷, AN(CH₂CH₂)₂O, AOR⁶ ou CH₂-phényle ;
- R² représente R⁶, Ar², Ar²CH=CH, Ar²CH(OH)CH₂, CHO, CN, CH₂OH, CH₂OR⁶, CH₂CH₂N-(CH₂CH₂)₂NR⁶, NH₂, NHR⁶ ou NR⁶R⁷,
- R³ représente hydrogène, alkyle linéaire ou ramifié en C₁-C₁₂, alcényle ou alcynyle linéaire ou ramifié en C₃-C₆, cycloalkyle en C₃-C₆, alkyle en C₁-C₆ substitué par cycloalkyle en C₃-C₆, AOR⁶, AO(CH₂)_mAr² (où m représente un entier de 0 à 3), (CH₂)_mAr², ANH₂, ANHR⁶, ANR⁶R⁷, ANR⁶(CH₂)_mAr², AN{(CH₂)_mAr²}{(CH₂)_nAr³} (où n a la même signification que m, et Ar³ a la même signification que Ar²), 1-benzyl-4-pipéridinyle, 1-benzyl-2-pipéridinyle, 2-pyridinylméthyle, 3-pyridinylméthyle, AQ (où Q représente pyrrolidine ou pipéridine qui peut être substitué par (CH₂)_mAr²), 4-R⁶-1-pipérazinyle, 4-Ar²-1-pipérazinyle, 4-(Ar²)₂CH-1-pipérazinyle ou 4-(Ar²)₂CH-1-(1,4-diazacycloheptyle);

ou d'un sel pharmaceutiquement acceptable du composé, pour la fabrication d'un agent destiné à rehausser l'effet médicamenteux d'un médicament anti-tumoral.

2. Utilisation selon la revendication 1, dans laquelle n'importe lequel des substituants R¹, R², R³, R⁴ et R⁵ dans le composé de la formule (I) contient au moins un atome d'azote basique capable de former un sel.

3. Utilisation d'un composé de la formule (III) :



dans laquelle :

- Ar¹ représente phényle, pyridyle, furyle ou 2,1,3-benzooxadiazol-4-yle, qui peut être substitué par un ou deux substituants choisis dans le groupe constitué par : NO₂, CF₃, Br, Cl, F, R⁶ (où R⁶ représente alkyle en C₁-C₄), OH, OR⁶, OCHF₂, COOR⁶, NH₂, NHR⁶, NR⁶R⁷ (où R⁷ a la même signification que R⁶), CONH₂, CONHR⁶, CONR⁶R⁷, COSR⁶, SR⁶, S(O)R⁶, S(O)₂R⁶, SO₃H, SO₃R⁶, SO₂NH₂, SO₂NHR⁶, SO₂NR⁶R⁷, CN et phényloxy ;
- Z représente un groupe de la formule (II) :



dans laquelle R⁴ et R⁵, qui peuvent être identiques ou différents, représentent chacun OH, alkyloxy, primaire ou secondaire, linéaire ou ramifié, en C₁-C₁₂, alcényloxy ou alcynyoxy linéaire ou ramifié en C₃-C₆, cycloalkyloxy en C₃-C₆, alcoxy en C₁-C₆ substitué par cycloalkyle en C₃-C₆, OAr² (où Ar² représente phényle qui peut être substitué par halogène, alkyle en C₁-C₃ ou alcoxy en C₁-C₃), OANR⁶R⁷ (où A représente alkylène en C₂-C₆ qui peut être substitué par alkyle en C₁-C₃ ou Ar²), OAN(CH₂Ar²)R⁶, OAOR⁶, OACN, NH₂, NHR⁶, NR⁶R⁷, 1-pipéridinyle ou 1-pyrrolidinyle, ou bien

R⁴ et R⁵ forment ensemble OYO (où Y représente alkylène linéaire en C₂-C₄ qui peut être substitué par R⁶, CO₂R⁶, OR⁶ ou A), NHYO, R⁶ NYO, NHYNH, R⁶ NYNH ou R⁶ NYNR⁷, ou Z représente CO₂R⁸ (où R⁸ a la même signification que R³ défini ci-après) ;

- R² représente R⁶, Ar², Ar²CH=CH, Ar²CH(OH)CH₂, CHO, CN, CH₂OH, CH₂OR⁶, CH₂CH₂N-(CH₂CH₂)₂NR⁶, NH₂, NHR⁶ ou NR⁶R⁷,
- R³ représente hydrogène, alkyle linéaire ou ramifié en C₁-C₁₂, alcényle ou alcynyle linéaire ou ramifié en C₃-C₆, cycloalkyle en C₃-C₆, alkyle en C₁-C₆ substitué par cycloalkyle en C₃-C₆, AOR⁶,

5. $AO(CH_2)_mAr^2$ (où m représente un entier de 0 à 3), $(CH_2)_mAr^2$, ANH_2 , $ANHR^5$, ANR^5R^7 , $ANR^5-(CH_2)_mAr^2$, $\{AN(CH_2)_mAr^2\}\{(CH_2)_nAr^3\}$ (où n a la même signification que m, et Ar^3 a la même signification que Ar^2), 1-benzyl-4-pipéridinyle, 1-benzyl-2-pipéridinyle, 2-pyridinylméthyle, 3-pyridinylméthyle, AQ (où Q représente pyrrolidine ou pipéridine qui peut être substitué par $(CH_2)_mAr^2$), 4- R^5 -1-pipérazinyle, 4- Ar^2 -1-pipérazinyle, 4- $(Ar^2)_2CH$ -1-pipérazinyle ou 4- $(Ar^2)_2CH$ -1-(1,4-diazacycloheptyle);
ou d'un sel pharmaceutiquement acceptable du composé par la fabrication d'un agent destiné à rehausser l'effet médicamenteux d'un médicament anti-tumoral.

10 4. Utilisation selon la revendication 3, dans laquelle n'importe lequel des substituants R^1 , R^2 , R^3 , R^4 et R^5 dans le composé de la formule (I) contient au moins un atome d'azote basique capable de former un sel.

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